Timing of delivery for women with non-severe hypertensive disorders of pregnancy

Broekhuijsen, Kim

Chapter 6

Prediction of progression to severe disease in women with late preterm hypertensive disorders of pregnancy

Submitted

Eva F. Zwertbroek
Kim Broekhuijsen
Josje Langenveld
Gert-Jan van Baaren
Paul P. van den Berg
Henk. A. Bremer
Wessel Ganzevoort
Aren. J. van Loon
Ben-Willem J. Mol
Maria G. van Pampus
Denise A.M. Perquin
Robbert J.P. Rijnders
Hubertina C.J. Scheepers
J.M. (Marko) Sikkema
Mallory D. Woiski
Henk Groen
Maureen T.M. Franssen
HYPITAT-II study group

Abstract

Introduction If hypertensive disorders of pregnancy (HDP) are diagnosed before term, the benefits of immediate delivery need to be weighed against the neonatal consequences of preterm delivery. If we are able to predict which women are at high risk of progression to severe disease, they could be targeted for delivery and maternal complications may be reduced. In addition, this may prevent unnecessary preterm births in women at low risk.

Methods We developed a prediction model using data from the HYPITAT-II trail, which evaluated immediate delivery versus expectant monitoring in women with HDP between 34 and 37 weeks of gestation. For the prediction model univariable and multivariable logistic regression analysis were used to identify relevant variables from clinical and laboratory parameters. The performance of the model was assessed by ROC analysis, calibration and bootstrapping, using the average predicted probabilities.

Results We included 519 women of whom 115 (22,2%) developed severe HDP. The prediction model included: maternal age (OR 0.92 per year), gestational age (OR 0.87 per week), systolic blood pressure (OR 1.05 per mmHg), the presence of chronic hypertension (OR 2.4), platelet count (OR 0.996), creatinin (OR 1.02) and LDH (OR 1.003). The model showed good fit ($p = 0.64$), fair discrimination (AUC 0.76, 95%CI 0.73 – 0.81, $p < 0.001$) and could stratify women in three risk groups of average, intermediate and high risk (predicted probabilities < 0.22, < 0.44 and > 0.45 respectively).

Conclusion In women with hypertension in pregnancy near term, progression to severe disease can be predicted.

Introduction

Hypertensive disorders of pregnancy (HDP) include chronic hypertension (CH), gestational hypertension (GH) and preeclampsia (PE), the latter either new-onset or superimposed in women with pre-existing (chronic) hypertension (superimposed PE, sPE). To date, these disorders complicate approximately 10% of all pregnancies.[1] Hypertensive disorders are very strongly associated with maternal morbidity and mortality such as eclampsia, placental abruption, and the syndrome of Hemolysis, Elevated Liver enzymes and Low Platelets (HELLP). In addition they are associated with neonatal morbidity, mainly due to iatrogenic preterm birth.[2]

Delivery is the only effective treatment option to prevent maternal or fetal complications in hypertensive disorders of pregnancy. For women with HDP at term, delivery is considered the management strategy of choice, given the similar risk of neonatal complications and improved maternal outcomes compared to expectant management.[3] However, preterm delivery may result in short term neonatal morbidity such as respiratory distress syndrome, or morbidity beyond the neonatal period such as neurological developmental problems, school related problems and impaired growth.[4] Therefore, if HDP are diagnosed before term, the benefits of delivery need to be weighed against the consequences of preterm delivery.

The HYPITAT-II study demonstrated a small, but statistically non-significant decrease in severe adverse maternal outcome after routine delivery of women with late preterm HDP (between 34 and 37 weeks of gestation). However, routine delivery significantly increased the risk of neonatal respiratory distress syndrome.[5]

It remains unclear whether expectant monitoring is the best management strategy for all women with late preterm hypertensive disorders; delivery might be beneficial in subgroups with a high risk of developing severe disease or for those with a more advanced gestational age. If women at high risk of progression to severe disease could be identified and targeted for delivery, maternal complications may be further reduced, while at the same time this may prevent unnecessary preterm births in women at low risk.[6]

Several (candidate) predictors of maternal morbidity in women with hypertensive disorders of pregnancy have been studied.[7-11] However, the prognostic value of a

combination of indicators for women with late preterm hypertensive disorders of pregnancy is unclear. Therefore, we assessed the capacity of clinical features and laboratory findings to predict progression to severe disease as indication for delivery among women with late preterm hypertensive disorders of pregnancy who are monitored expectantly.

Methods

STUDY POPULATION

We used data from women who were monitored expectantly in the HYPITAT-II trial. This was a multi-center, randomized controlled trial, comparing immediate delivery to expectant monitoring for women with late preterm hypertensive disorders. It was performed in the Netherlands between March 2009 and March 2013. The trial was approved by the Institutional Review Board of the Academic Medical Centre in Amsterdam (08/244), and had local approval from the boards of the other participating hospitals. The inclusion criteria of HYPITAT-II were a pregnancy complicated by gestational hypertension, preeclampsia, deteriorating chronic hypertension, or superimposed preeclampsia, and a gestational age from 34^{+0} up to and including 36^{+6} weeks. Gestational hypertension was defined as a diastolic blood pressure (BP) ≥ 100 mmHg measured at two occasions at least six hours apart. Preeclampsia was defined as a diastolic BP ≥90 mmHg and proteinuria. Proteinuria was defined as ≥ 300 mg total protein in a 24h urine collection or a spot protein-creatinin ratio of ≥ 30 mg/mmol (PCR). Women with chronic hypertension (defined as blood pressure ≥ 140/90 mmHg before 20 weeks of gestation[12] could be included if they had either superimposed preeclampsia (defined as new onset of proteinuria) or deteriorating hypertension (defined as the need for new/additional antihypertensive medication after 34 weeks). Exclusion criteria were maternal age <18 years, the presence of severe hypertensive disorder (diastolic BP ≥ 110 mmHg and/or systolic BP ≥ 170 mmHg despite medication, proteinuria ≥ 5g/L), HELLP syndrome, renal or heart disease, HIV seropositivity, pulmonary edema or cyanosis, non-reassuring fetal heart rate, fetal abnormalities including abnormal karyotype, and ruptured membranes.

After informed consent women were randomized to either a policy aimed at delivery (intervention group) or a policy aimed at expectant monitoring until 37 weeks

of gestation (expectant group). Women in the expectant group were monitored until 37 weeks of gestation or until an indication for delivery occurred, whichever occurred earlier. Monitoring consisted of frequent maternal BP measurements, assessments of proteinuria, laboratory tests and regular assessment of the fetal condition. Women who declined randomisation were asked for informed consent to collect data from their medical files (observational arms); their treatment was at the discretion of the attending obstetrician. For the current analysis we focussed on the combined group of randomized as well as non-randomized women who underwent expectant monitoring.

OUTCOME MEASURES

The primary endpoint for the current study was progression to severe disease as indication for delivery. This endpoint was chosen considering it is more relevant to the clinician to predict which women will develop an indication for delivery, than to predict which women will develop adverse outcomes regardless of clinical management.

Severe hypertensive disorder as indication for delivery was defined as the occurrence of any of the following indications for delivery: a diastolic blood pressure ≥ 110 mmHg despite medication, a systolic blood pressure ≥ 160 mmHg despite medication, eclampsia, HELLP syndrome (platelet count <100 x 109/L, AST > 70 U/L or ALT > 70 U/L, and LDH > 600 U/L), anuria (defined as a urinary production <30 ml/hour lasting ≥4 hours), pulmonary edema, or severe preeclamptic complaints.[12,13,15,16] Women who were recorded to have "severe HDP" as indication for delivery but who did not have any of the defining characteristics of severe HDP as listed in the protocol were assessed on an individual basis by the study group.

We evaluated whether our primary outcome measure (HDP indication for delivery) could be predicted with several characteristics at hospital admission. Candidate predictors were selected based on previous studies.[3,7,9-11,17-25] Selected predictors were maternal characteristics (ethnicity, maternal age, education, smoking), clinical characteristics (diastolic BP, systolic BP, body mass index, gravidity, parity, gestational age, previous abortion, previous caesarean section, type of HDP, history of HDP, comorbidity) and laboratory findings (proteinuria, Hb, Ht, platelets, creatinin, uric acid, ALT, AST, and LDH) measured at baseline.

Table 1. Baseline patient characteristics. Original data.

	Progression to severe disease as indication for delivery		No progression to severe disease as indication for delivery		*p* value
clinical characteristics		available		available	
nulliparous	71 (61.7%)	115 (100)	260 (64.4%)	404 (100)	0.580
gravidity	2 (1–5)	115 (100)	1 (1–5)	404 (100)	0.28
maternal age (years)	30 (22–38)	115 (100)	31 (23–40)	404 (100)	0.008
BMI (kg/m²)	31.1 (22.1–42.1)	64 (55.6)	30.8 (21.1–42.6)	191 (47.3)	0.584
gestational age (weeks)	34.1 (28.0–36.3)	112 (97.4)	35.0 (30.3–36.6)	399 (98.8)	0.003
No. of fetus		115 (100)		404 (100)	0.205
singleton	105 (91.3%)		383 (94.6%)		
twin	10 (8.7%)		22 (5.4%)		
smoking	20 (17.7%)	113 (98.3)	50 (12.9%)	389 (96.3)	0.192
blood pressure (mmHg)					
systolic BP	148 (125–170)	115 (100)	140 (122–160)	404 (100)	0.000
Diastolic BP	95 (85–110)	115 (100)	95 (80–105)	404 (100)	0.015
laboratory findings					
proteinuria	68 (98.6%)	70 (60.9)	240 (93%)	258(63.9)	0.113
no proteinuria	1 (1.4%)		18 (7.0%)		
PCR ratio (mg/mmol)	52 (13.4–821.8)	47 (40.9)	40 (3.6–405)	171 (42.3)	0.087
24 hours proteinuria (mg)	600 (8.6–4378.5)	58 (50.4)	400 (0–2586)	243 (60.1)	0.003
dipstick		73 (63.5)		236 (58.4)	0.068
trace	9 (12.3%)		44 (18.6%)		
+	17 (23.3%)		67 (28.4%)		
++	17 (23.3%)		52 (22.0%)		
+++	16 (21.9%)		22 (9.3%)		
hemoglobin (mmol/L)	7.5 (6.1–8.7)	115 (100)	7.5 (6.3–8.6)	403 (99.8)	0.537
hematocrite (L/L)	0.36(0.29–0.42)	108 (93.9)	0.36 (0.30–0.41)	353 (87.4)	0.182
platelets (*10^9/L)	194 (124–317)	115 (100)	219 (129–331)	402 (99.5)	0.008
creatinin (µmol/L)	58 (44–86)	114 (99.1)	56 (40–80)	399 (98.8)	0.043
uric acid (mmol/L	0.35 (0.21–0.48)	110 (95.7)	0.32(0.19–0.46)	377 (93.3)	0.011
ALAT (U/L)	13.0 (6.6–54.3)	110 (95.7)	14.0(6.0–40.3)	366 (90.6)	0.737
ASAT (U/L)	21.0 (10.6–63.0)	91 (79.1)	19.0 (10.0–44.4)	303(75.0)	0.351
LDH (U/L)	210.0 (137.5–457.2)	108 (93.3)	194.0 (134.0–390.9)	353 (87.4)	0.012
social economic					
Caucasian	96(85.0%)	113(98)	336 (85.9%)	391 (96.8)	0.794
Non-Caucasian	17(15.0%)		55 (14.1%)		
higher education	31 (40.3%)	77 (67)	117(46.8%)	250 (61.9)	0.314
lower education	46 (59.7%)		133 (53.2%)		
medical history					
preeclampsia	18 (15.7%)	115 (100)	52 (12.9%)	403 (99.8)	0.448
caesarean section	12 (10.5%)	114 (99.1)	41 (10.2%)	404 (99.8)	0.900
abortion	38 (33.3%)	114 (99.1)	114 (28.2%)	404 (100)	0.290
comorbidity					
yes	31 (27.7%)	112 (97.4)	85 (21.5%)	395 (97.8)	0.172

Table 1. continued

	Progression to severe disease as indication for delivery		No progression to severe disease as indication for delivery		*p* value
clinical characteristics		available		available	
no	81 (72.3%)		310 (78.5%)		
diabetes mellitus	2 (1.7%)	115 (100)	5 (1.2%)	404 (100)	0.682
diabetes mellitus gravidarum	5 (4.3%)	115 (100)	9 (2.2%)	404 (100)	0.224
diagnosis					
gestational hypertension	23 (20.0%)	115 (100)	109 (27.0%)	404 (100)	0.000
preeclampsia	39 (33.9%)		187 (46.3%)		
chronic hypertension	53 (46.1%)		108 (26.7%)		

Data are no (%) or median (5th–95th percentile)

SAMPLE SIZE

In the HYPITAT-II study, 703 women were randomised, while 176 women participated in the observational arms. The current study population consisted of a convenience sample of 519 from these women: all 351 women who were randomized to the expectant monitoring group and all 168 non-randomized women who opted for expectant monitoring. With the observed prevalence of an indication for delivery, this sample size was sufficient to study up to 10 predictors.

MISSING DATA

Our primary outcome measure, progession to severe HDP as indication for delivery, had no missing data. However, a few candidate prognostic variables did have a percentage of missing values >5%. Exclusion of cases with missing values would have led to loss of statistical power in the multivariable approach and, more seriously, potentially biased results.[26] Therefore, we used multiple imputation to handle these missing values.[27] Ten multiply imputed datasets were generated using predictive mean matching.

STATISTICAL ANALYSIS

Firstly, descriptive statistics were generated using PASW Statistics 22.0 (SPSS inc.). Secondly, univariable logistic regression was performed to assess the predictive value of all candidate predictors, using the imputed datasets. Next, we calculated pooled odds ratios, 95% confidence intervals and p values from the ten datasets. Then, predictors with a p value <0.157 were selected for the multivariable logistic regression analysis.[27] We used backward stepwise selection to generate the prediction model.[27] The model performance was assessed by calibration and the

Hosmer-Lemeshow test for goodness of fit, with p-values closer to one indicating better fit. To evaluate the discriminative performance the model the area under the receiver-operating characteristic (ROC) curve was calculated using the predicted and the actual outcome. The mean predicted probabilities were calculated across the ten imputations. The calibration of the model was then assessed by plotting observed and predicted events for 10 subgroups of women based on deciles of the predicted probability of severe disease. In every subgroup the mean predicted and mean observed probability were calculated. If the predicted probability equals the observed probability all points would be on the line x = y and the calibration would be perfect. The model was internally validated with bootstrapping using R-project software 3.0.2. (2013).

Results

Between March 2009 and March 2013, 897 women were included in the HYPITAT II trial. A total of 519 women were included fort he current analysis: 351 (39.0%) who were randomized to expectant monitoring and 168 (18.8%) women who were monitored expectantly in the observational arm of the study. From this selection, 163 (31%) women had gestational hypertension, 292 (56%) had preeclampsia and 64 (12%) women had chronic hypertension at inclusion. Progression to severe disease was the indication for delivery in 115 (22%) women.

Baseline characteristics comparing women with and without development of severe HDP as indication for delivery are presented in table 1. Women who progressed to severe disease were significantly younger (OR 0.95, 95% CI 0.91–0.99) and had a significantly lower gestational age (OR 0.89, 95% CI 0.82–0.96) compared to women who did not. Women with chronic hypertension were more likely to develop severe HDP when compared to women with preeclampsia or gestational hypertension (OR 2.3, 95% CI 1.5–3.6), while women with preeclampsia were in turn more likely to develop severe HDP compared to women with gestational hypertension. Women who developed severe HDP had higher systolic (OR 1.04, 95% CI 1.02–1.06) and diastolic (OR 1.04, 95% CI 1.01-1.07) blood pressures, and had more severe proteinuria as measured in 24-hour urine collections (OR 1.000, 95% CI 1.000–1.001). With regard to laboratory findings, lower levels of platelets (OR 0.995, 95% CI 0.992–0.999) and creatinin (OR 1.02, 95% CI 1.00–1.03) and

higher levels of uric acid (OR 30, 95% CI 2.2–423) and LDH (OR 1.003, 95% CI 1.001–1.005) were associated with progression to severe HDP.

Table 2 shows the pooled results of the univariable analyses of the imputed datasets. Table 3 shows the predictors included in the final model after stepwise backward selection: maternal age, presence of co-morbidity, diagnosis of chronic hypertension, gestational age in weeks, systolic blood pressure, platelet count, creatinin, LDH, and presence of proteinuria, all measured at inclusion. The Hosmer-Lemeshow test for goodness of fit showed a good fit of the model ($p = 0.642$). The ROC-curve is presented in figure 1. It showed fair discriminative performance (AUC 0.76, 95% CI 0.73–0.81, $p < 0.001$). With regard to calibration (figure 2) the model slightly overestimated the risk for the probabilities ranging from zero to 0.1. In terms of risk stratification, three groups could be identified, carrying a different risk of progression to severe hypertensive disorder as an indication for delivery. In the first six deciles, according to predicted probability (0.018 to 0.220), the observed probability did not exceed the overall risk of 22%. The 7th, 8th and 9th decile can be considered the intermediate risk group with a predicted probability ranging from 0.221 to 0.444. The 10th decile, with a predicted probability of 0.449 or higher, can be regarded as high risk. The mean risk of women in the high risk group was 0.589. Bootstrapping showed that the overfitting was minimal (the AUC was only 2-3% smaller than with the original data), indicating that the model holds for the overall population.

Discussion

We developed a unique model to predict progression of HDP as indication for delivery among women with late preterm HDP. The results of our study demonstrate that the model can discriminate women with a high risk of developing severe disease can be discriminated from women at lower risk. The final model included maternal age, presence of co-morbidity, diagnosis of chronic hypertension, gestational age in weeks, systolic blood pressure, presence of proteinuria, platelets, creatinin and LDH.

Table 2. Results of the univariable analysis of predictors of progression to severe disease as indication for delivery, pooled estimates based on imputed data.

	OR	95% CI	*p* value
clinical characteristics			
multiparous	1.119	0.730–1.716	0.607
gravidity			0.280
maternal age (years)	0.945	0.906–0.985	0.008
BMI	1.019	0.977–1.062	0.370
gestational age (weeks)	0.890	0.822–0.963	0.004
no. of fetus	1.654	0.760–3.601	0.205
smoking	1.454	0.827–2.557	0.193
blood pressure (mmHg)			
systolic BP	1.041	1.022–1.060	0.000
diastolic BP	1.037	1.007–1.068	0.015
laboratory findings			
significant proteinuria	1.808	1.017–3.214	0.044
PCR	1.255	1.025–1.538	0.028
24 hours proteinuria	1.098	0.962–1.255	0.161
dipsticks (vs. negative)			
trace	0.647	0.264–1.583	0.337
+	0.808	0.394–1.657	0.559
++	1.075	0.475–2.429	0.861
+++	2.237	0.963–5.195	0.061
hemoglobin	0.913	0.683–1.220	0.539
hematocrite	0.045	0.000–30.038	0.350
platelets	0.995	0.992–0.999	0.008
creatinin	1.016	1.001–1.030	0.035
uric acid	23.813	1.687–336.115	0.019
ALAT	1.002	0.992–1.011	0.756
ASAT	1.006	0.995–1.017	0.289
LDH	1.003	1.001–1.005	0.015
social economic			
caucasian	0.918	0.209–1.656	0.776
high education	0.850	0.523–1.271	0.366
medical history			
preeclampsia	1.245	0.696–2.227	0.460
cesarean section	1.098	0.560–2.153	0.785
abortion	1.270	0.813–1.984	0.293
comorbidity	1.411	0.875–2.275	0.158
diabetes mellitus gravidarum	1.995	0.655–6.074	0.224
diabetes mellitus	1.412	0.270–7.377	0.682
diagnosis			
chronic hypertension	2.343	1.527–3.594	0.000
gestational hypertension	0.677	0.408–1.123	0.131

Table 3 Multivariate analysis of predictors of progression to severe disease requiring delivery, pooled estimates based on imputed data.

	Odds ratio	95% CI	*p* value
clinical characteristics			
maternal age	0.919	0.876–0.961	0.000
gestational age (weeks)	0.874	0.799–0.957	0.004
systolic BP	1.046	1.025–1.067	0.000
comorbidity	1.519	0.890–2.593	0.126
chronic hypertension	2.371	1.466–3.833	0.000
laboratory findings			
significant proteinuria	1.769	0.920–3.401	0.087
platelets	0.996	0.992–1.000	0.034
creatinin	1.015	0.998–1.032	0.078
LDH	1.003	1.000–1.006	0.034

This study has several strengths and limitations. Data were derived from a large multicenter study including participants from a large number of hospitals throughout the Netherlands. Therefore we believe that this group is representative for women with hypertensive disorders of pregnancy between 34-37 weeks of gestation, which is a strength. The various numbers of missing values were a limitation. For the multivariable approach these missing values were imputed to avoid loss of statistical power and, more seriously, biased results. With regard to proteinuria, both PCR and 24 hours proteinuria had missing values, indicating that both of these techniques are used in the Netherlands to determine whether significant proteinuria is present. Therefore we used the dichotomous variable 'significant proteinuria' yes or no, based on widely accepted thresholds.

This model, based on routinely available parameters in a developed world situation, showed good fit and fair discrimination. However, the model slightly overestimated the risk for the probabilities ranging from zero to 0.1. For this very low risk the overestimation will not be a problem because the observed risk is still very low. The model identified three categories of women at average, intermediate and high risk of progression to severe hypertensive disorder as indication for delivery. The overall risk of developing severe disease as an indication for delivery was 22%. Since the thresholds for medium and high risk categories are above this average risk, the model is very useful to distinguish the medium and high risk group from the low risk group. This is also very relevant because 40% of the women with HDP had a higher risk than the average of progression to severe HDP.

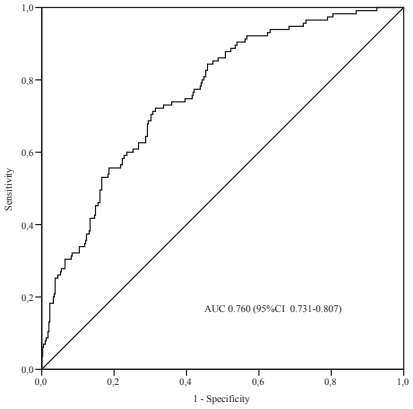

Figure 1. Receiver-operating characteristic graph of prediction model for progression to severe disease, calculated by multivariable analysis

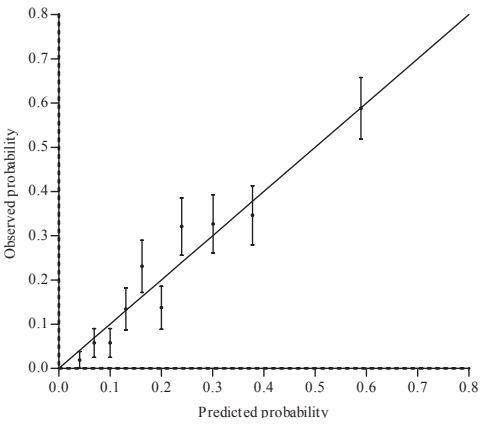

Figure 2. Calibration plot demonstrating the association between the estimated and actual risks of progression to severe disease as indication for delivery, pooled estimates based on imputed data

Our model was not the first model designed to predict severe disease of HDP. Von Dadelszen et al. developed a model to predict adverse outcomes.[9] As opposed to our model, subjective maternal symptoms were included in their model. These were not available in the HYPITAT-II data. However, maternal symptoms are non-quantifiable parameters and therefore the model would probably be more exact by not using these as predictors.[17,19-21,23] The type of hypertensive disorder was not frequently used as predictor in other prediction models and chronic hypertension was not considered a risk factor or an important predictor of severe disease until now. However, in our analysis, chronic hypertension was one of the strongest predictors of severe disease. Therefore this predictor should be taken into account in the management of hypertensive disorders in pregnancy.

In clinical practice, this model can assist clinicians to stratify women in categories of average, intermediate and high risk. Women at average risk (ranging from 0.018 to 0.220) can be monitored according to current regular care. For the intermediate risk group (ranging from 0.221 to 0.444), more frequent monitoring or cervical ripening in case of an unripe cervix could be considered. The probability of developing severe disease in the high risk group ranged from 0.449 to 0.964 and the mean risk was 0.589. In this selected 10% of the population, immediate delivery could be considered, since the risk of severe maternal disease is 60% while the risk of neonatal respiratory distress syndrome for immediate delivery would be 5.7%.[5] In these cases, the maternal benefits of delivery may outweigh the risk of the

neonatal consequences of preterm delivery. Based on our data, no recommendations regarding less frequent monitoring in the average risk group can be made, since our prediction is based on the current standard of monitoring.

Further research needs to be done to validate the model externally. We plan to test the model on international data and, eventually, to prospectively evaluate implementation in Dutch clinics. Furthermore, angiogenic factors could not be considered as predictors; these factors only emerged as possible predictors for developing complications in women with HDP during recruitment of the HYPITAT-II study, and they were not measured. However we recommend to investigate these factors in future studies on hypertensive disease in pregnancy in combination with clinical and laboratory parameters to predict maternal severe disease late preterm. Nevertheless, until angiogenic factors have been studied sufficiently, our model based on routinely available parameters is of relevance.

In conclusion, HYPITAT-II results showed that immediate delivery cannot be recommended for all women who developed hypertensive disorders of pregnancy during late preterm pregnancy (34-37 weeks of gestation): any decrease in the risk of adverse maternal outcomes was likely to be small, while the risk of neonatal RDS increased significantly. As delivery might be beneficial in subgroups of women with a high risk of developing severe disease, we developed a unique model to predict the progression of HDP between 34 and 37 weeks of pregnancy. It stratifies women in groups of low, medium and high risk. After external validation, this model has the potential to help clinical decision making and to prevent unnecessary interventions or preventable progression to severe disease.

References

1 Hutcheon JA, Lisonkova S, Joseph KS. Epidemiology of pre-eclampsia and the other hypertensive disorders of pregnancy. Best Pract Res Clin Obstet Gynaecol 2011 Aug;25(4):391-403.

2 Abalos E, Cuesta C, Carroli G, Qureshi Z, Widmer M, Vogel JP, et al. Pre-eclampsia, eclampsia and adverse maternal and perinatal outcomes: a secondary analysis of the World Health Organization Multicountry Survey on Maternal and Newborn Health. BJOG 2014 Mar;121 Suppl 1:14-24.

3 Koopmans CM, Bijlenga D, Groen H, Vijgen SM, Aarnoudse JG, Bekedam DJ, et al. Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation (HYPITAT): a multicentre, open-label randomised controlled trial. Lancet 2009 Sep 19;374(9694):979-988.

4 Teune MJ, Bakhuizen S, Gyamfi Bannerman C, Opmeer BC, van Kaam AH, van Wassenaer AG, et al. A systematic review of severe morbidity in infants born late preterm. Am J Obstet Gynecol 2011 Oct;205(4):374.e1-374.e9.

5 Broekhuijsen K, van Baaren GJ, van Pampus MG, Ganzevoort W, Sikkema JM, Woiski MD, et al. Immediate delivery versus expectant monitoring for hypertensive disorders of pregnancy between 34 and 37 weeks of gestation (HYPITAT-II): an open-label, randomised controlled trial. Lancet 2015 Mar 24.

6 Holland MG, Refuerzo JS, Ramin SM, Saade GR, Blackwell SC. Late preterm birth: how often is it avoidable? Am J Obstet Gynecol 2009 Oct;201(4):404.e1-404.e4.

7 Martin JN,Jr, May WL, Magann EF, Terrone DA, Rinehart BK, Blake PG. Early risk assessment of severe preeclampsia: admission battery of symptoms and laboratory tests to predict likelihood of subsequent significant maternal morbidity. Am J Obstet Gynecol 1999 Jun;180(6 Pt 1):1407-1414.

8 Koopmans CM, van Pampus MG, Groen H, Aarnoudse JG, van den Berg PP, Mol BW. Accuracy of serum uric acid as a predictive test for maternal complications in pre-eclampsia: bivariate meta-analysis and decision analysis. Eur J Obstet Gynecol Reprod Biol 2009 Sep;146(1):8-14.

9 von Dadelszen P, Payne B, Li J, Ansermino JM, Broughton Pipkin F, Cote AM, et al. Prediction of adverse maternal outcomes in pre-eclampsia: development and validation of the fullPIERS model. Lancet 2011 Jan 15;377(9761):219-227.

10 Menzies J, Magee LA, Macnab YC, Ansermino JM, Li J, Douglas MJ, et al. Current CHS and NHBPEP criteria for severe preeclampsia do not uniformly predict adverse maternal or perinatal outcomes. Hypertens Pregnancy 2007;26(4):447-462.

11 Thangaratinam S, Coomarasamy A, O'Mahony F, Sharp S, Zamora J, Khan KS, et al. Estimation of proteinuria as a predictor of complications of pre-eclampsia: a systematic review. BMC Med 2009 Mar 24;7:10-7015-7-10.

12 Nederlandse vereniging voor obstetrie en gynaecologie. Richtlijn hypertensieve aandoeningen in de zwangerschap. 2011; Available at: http://nvog-documenten.nl/uploaded/docs/Hypertensieve%20aandoeningen%20in%20de%20zwangerschap.pdf. Accessed may/1, 2014.

13 American College of Obstetricians and Gynecologists, Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013 Nov;122(5):1122-1131.

14 National Collaborating Centre for Women's and Children's Health (UK). 2010 Aug.

15 Lowe SA, Brown MA, Dekker GA, Gatt S, McLintock CK, McMahon LP, et al. Guidelines for the management of hypertensive disorders of pregnancy 2008. Aust N Z J Obstet Gynaecol 2009 Jun;49(3):242-246.

16 Magee LA, Helewa M, Moutquin JM, von Dadelszen P, Hypertension Guideline Committee, Strategic Training Initiative in Research in the Reproductive Health Sciences (STIRRHS) Scholars. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. J Obstet Gynaecol Can 2008 Mar;30(3 Suppl):S1-48.

17 van der Tuuk K, Koopmans CM, Groen H, Aarnoudse JG, van den Berg PP, van Beek JJ, et al. Prediction of progression to a high risk situation in women with gestational hypertension or mild pre-eclampsia at term. Aust N Z J Obstet Gynaecol 2011 Aug;51(4):339-346.

18 Morris RK, Riley RD, Doug M, Deeks JJ, Kilby MD. Diagnostic accuracy of spot urinary protein and albumin to creatinine ratios for detection of significant proteinuria or adverse pregnancy outcome in patients with suspected pre-eclampsia: systematic review and meta-analysis. BMJ 2012 Jul 9;345:e4342.

19 Nisell H, Palm K, Wolff K. Prediction of maternal and fetal complications in preeclampsia. Acta Obstet Gynecol Scand 2000 Jan;79(1):19-23.

20 Caetano M, Ornstein MP, von Dadelszen P, Hannah ME, Logan AG, Gruslin A, et al. A survey of canadian practitioners regarding diagnosis and evaluation of the hypertensive disorders of pregnancy. Hypertens Pregnancy 2004;23(2):197-209.

21 von Dadelszen P, Magee LA, Devarakonda RM, Hamilton T, Ainsworth LM, Yin R, et al. The prediction of adverse maternal outcomes in preeclampsia. J Obstet Gynaecol Can 2004 Oct;26(10):871-879.

22 Waugh J, Bell SC, Kilby MD, Lambert P, Shennan A, Halligan A. Urine protein estimation in hypertensive pregnancy: which thresholds and laboratory assay best predict clinical outcome? Hypertens Pregnancy 2005;24(3):291-302.

23 Ganzevoort W, Rep A, de Vries JI, Bonsel GJ, Wolf H, PETRA-investigators. Prediction of maternal complications and adverse infant outcome at admission for temporizing management of early-onset severe hypertensive disorders of pregnancy. Am J Obstet Gynecol 2006 Aug;195(2):495-503.

24 Thangaratinam S, Ismail KM, Sharp S, Coomarasamy A, Khan KS, Tests in Prediction of Pre-eclampsia Severity review group. Accuracy of serum uric acid in predicting complications of pre-eclampsia: a systematic review. BJOG 2006 Apr;113(4):369-378.

25 Thangaratinam S, Ismail K, Sharp S, Coomarasamy A, O'Mahony F, Khan KS, et al. Prioritisation of tests for the prediction of preeclampsia complications: a Delphi survey. Hypertens Pregnancy 2007;26(1):131-138.

26 Steyerberg EW, Harrell FE,Jr, Borsboom GJ, Eijkemans MJ, Vergouwe Y, Habbema JD. Internal validation of predictive models: efficiency of some procedures for logistic regression analysis. J Clin Epidemiol 2001 Aug;54(8):774-781.

27 Royston P, Moons KG, Altman DG, Vergouwe Y. Prognosis and prognostic research: Developing a prognostic model. BMJ 2009 Mar 31;338:b604.

Part II

General aspects of delivery versus expectant monitoring for women with non-severe hypertensive disorders of pregnancy